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10/626,772	07/25/2003	Kazutomo Inoue	0020-5157P	1689

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,772	INOUE ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *7,8,11 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/25/03;8/21/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-14 are pending.

Election/Restrictions

Applicant's election without traverse of group I, claims 5, 6, 10, 12 and 13 in the reply filed on 3/17/06 is acknowledged.

Claims 7-8, 11, 14 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/17/06.

Claims 1-6, 9-10 and 12-13 are under consideration.

Claim Objections

2. Claims 2 and 9-10 are objected to because of the following informalities:

Claim 2 appears to embrace cultured conditions to give rise to (embryoid bodies). As written the claim suggests culture conditions for the creation of (embryonic bodies). Appropriate correction is required.

Claim 9 recites preamble "Functioning cells". As written it is grammatically incorrect as claim should begin with an article.

Claim 10 recites preamble "Insulin secreting cell clusters". As written it is grammatically incorrect as claim should begin with an article.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9-10 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-6 and 9-10 are directed to a method for inducing differentiation of mammalian embryonic stem cells into functioning cells wherein further embodiments limit the functioning cells into pancreatic islet like insulin secreting cell clusters.

Claims 12-13 are directed to a method of treating a mammalian patient including human having disorders in pancreatic islet function which comprises implanting pancreatic isle-like cell clusters induced from allogeneic ES cells.

The specification discusses that the invention features a method for inducing differentiation of pluripotent embryonic stem (ES) cells into functioning cells, especially pancreatic islet like cell clusters (specification p 7). The specification further discusses the transplantation of said pancreatic islet clusters into a mammalian patient having disorders in pancreatic islet function for treatment of diseases but not limited to type I and type II diabetes cystic fibrosis or pancreatomized patients (specification p 17). While the specification contemplates the production of said cells, the specification fails to provide any relevant teachings or specific guidance and/or working examples with regard to the production of

mammalian functional pancreatic islet like cell clusters and using said cells to treat any mammalian patient with said disorders by way of the claimed methods. The specification fails also to provide any other uses for the pancreatic islet like cell clusters. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the production of functional pancreatic islet like cell clusters for treating said pancreatic disorders. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

As a first issue, claims 1-6 and 9-10 are directed to an ex vivo method for inducing differentiation of mammalian embryonic stem (ES) cells into pancreatic islet like insulin secreting cell clusters. The specification discusses that in the present invention the term ES cells represents pluripotent cells derived from the inner mass of in vitro fertilized balstocysts from various species including human (specification p 10-11). While the specification disclosed the production of insulin producing cells derived from the established 129sv and C57/BL6 mouse ES cell lines by way of the claimed culture condition methods, the specification has failed to provide any specific guidance and/or working examples for the ex vivo production of functional mammalian pancreatic islet like insulin secreting cell clusters derived from mammalian pluripotent cells which are derived from the inner mass of in vitro blastocysts. Even though, the specification teaches the production of mouse pancreatic islet like insulin secreting cell clusters, however, the specification does not teach if the disclosed cells are functional in vitro, because the art teaches that, in order for the cells to be functional in vitro, for example, the cells need to be responsive to glucose and or other secretagogues. Therefore, functionality in vivo cannot be assessed. Otonkoski et al, (Annals of Medicine, 37: 513-520, 2005) reports that in spite of some promising results, it appears that many of the results published so far on mouse ESC differentiation towards a beta-cell like phenotype represent an aberrant differentiation pathway of neuroectodermally committed cells, and do not provide a platform for the generation of long-term viable and physiologically functioning beta-cells (p 517, 2nd column). Otonkoski et al, further reports that human ES cell research is still at an early stage and many principles established in mouse ESCs cannot be directly applied in human ESCs. Insulin has been detected in differentiating human embryoid bodies, but it is not clear if this reflects true pancreatic differentiation (p 517, 2nd column). Otonkoski et al, concluded that the importance of thorough phenotypic analysis of the cells obtained after the differentiation process should

include not only the demonstration of insulin protein but also evidence of C-peptide cleavage and the expression of key proteins needed for glucose sensing and regulating exocytosis, as well as functional analysis of insulin release induced by glucose and other secretagogues (p 518, 1st column).

In addition, human ESCs resistance to senescence is another limiting factor of culturing pancreatic islet like insulin secreting cell clusters. Halvorsen et al, (Journal of Endocrinology, 166: 103-109, 2000) reported accelerated telomere shortening and senescence in human pancreatic islet cells in vitro (title) and Betts et al (Developmental Genetics, 25:397-403, 1999) reported telomerase activity during early bovine development. Assady et al, (Diabetes, 50:1691- 1697, 2001) while reports insulin production by human ES cells also reports that limiting issue that may arise include senescence of postdifferentiation of human ES–cell derivatives attributed to loss of telomerase (p 1695 2nd column and p 1696 1st column).

Furthermore, the art teaches that many aspects of embryonic stem cell (ESC) biology need to be elucidated before stable differentiated cells are defined (Gjorret et al, Reproduction, Fertility and Development, 17: 113-124, 2005) (p 115, 1st column). One of the initial requirements is to define controlled and standardized procedures adequate for the establishment and maintenance of ESCs without any unintended alterations in their inherent properties. Unfortunately, ESCs may not be as intrinsically stable as desired. Epigenetic regulation of gene expression in murine ESCs appears to be variable among different subclones of the same ESCs line and evethough murine ESCs display a low tendency for spontaneous mutations, they seem to have an increased propensity to acquire chromosomal abnormalities compared to somatic cells in cultute (Gjorret et al, p 115, 2nd column). Gjorret et al, also noted that regrettably, this may also apply to human ESCs, in which specific chromosomal translocations have been observed on several occasions (Gjorret et al, p 115, 2nd column). An

additional facet that needs attention is the degree of in vitro differentiation efficiency at which this hazard becomes eradicated need to be defined as well as whether differentiation of ESCs follows one way street or is as reversible process at some stages (Gjorret et al, p 115, 2nd column). Madsen et al, (ARMIS, 113: 858-75, 2005) also reports that the major challenge for ES cells remains to be able to direct the in vitro differentiation of ES cells into a specific desired direction, at the same time preventing of suppressing all other irrelevant choices of the pluripotent repertoire (p 867, 1st column and figures 4 and 5).

As such the art of record clearly states the production of a functional mammalian pancreatic islet like insulin secreting cell clusters ex vivo is undeveloped and in its infancy at best. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations for the production of functional mammalian pancreatic islet like insulin secreting cell clusters by way of the claimed method. Therefore, the skilled artisan would conclude that the state of art of functional mammalian pancreatic islet like insulin secreting cell clusters is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing an ex vivo population of functional mammalian pancreatic islet like insulin secreting cell clusters without a reasonable expectation of success.

As a second issue, claim 12 is directed to a method for treating a mammalian patient having disorders in pancreatic islet function by implanting allogeneic pancreatic islet-like cell clusters wherein claim 13 limits the diseases to Type I diabetes. The specification teaches transplantation of mouse insulin producing cell clusters into streptozotocin (STZ) induced diabetic nude mice wherein all implanted mice remained healthy until killed and kept significantly lower blood glucose levels than the sham control group up to 18 days post transplantation (specification p 28-30, example 2 and figure 3). The specification also

contemplates the use of allogeneic human ES cells which are obtained as described by incorporated reference and thus obtained cell clusters produce insulin and secret insulin in response to glucose in a dose dependent manner wherein cell clusters are injected into liver via portal vein or are implanted to subcutaneous space as bio-artificial pancreas wherein the pancreatic function of the implanted patient is restored and the patient acquires independence from insulin (specification p 32 and example 4). While the specification has contemplated treating pancreatic disorders due to lack of pancreatic islet function and also treating type I diabetes of a mammalian patient by generating ex vivo allogeneic functional pancreatic islet-like cell clusters and implanting said cell clusters into a patient, the specification has failed to provide specific guidance and/or working examples correlating to treatment of said disorders by way of the claimed methods. This is so because the specification has failed to provide guidance and/or specific examples as to the functionality of said allogeneic pancreatic cell clusters after implantation, which will result in the treatment of claimed disorders in vivo. Even after the filing date of the instant application, Holland et al, (Diabetes/Metabolism Research and reviews, 20: 13027, 2004) teaches that to date, four studies have reported the generation insulin-positive cells from ES cells wherein these cells showed acceptable insulin responses to various secretagogues in vitro and were able to normalize blood glucose levels in STZ-induced diabetic mice (p 20, 1st and 2nd column). However, the ability of these cells to restore normoglycaemia in diabetic mice was not determined (Holland et al, p 20 second column). Holland et al, went on to say that although these islet clusters were able to release insulin in response to glucose and other insulin secretagogues in vitro, the level of insulin produced by these cells was low in comparison to normal islets, and when transplanted into STZ-induced diabetic mice they were unable to correct hypeglycaemia (Holland et al, p 20 second column).). Colman (Seminars in Cell & Developmental Biology, 15: 337-345, 2004) reports that assessment of in vivo function in

the surrogate cells is most frequently made using cell transplantation into beta cell toxin (STZ)-induced diabetic mice but this model is rarely used to maximal advantage (abstract). In many cases, it remains unclear whether reductions in the hyperglycemia result from insulin secretion from the transplanted cells or are due to recovery of endogenous islet function (abstract).

Another issue in allogeneic transplantation of pancreatic islet cell clusters into a mammalian patient is the issue of immune rejection. Soria et al, (Diabetes, 49: 1-6, 2000) noted that while the use of ES-derived cell opens new possibilities for tissue transplantation in the treatment of diabetes however, there are some problems to solve, such as tumor development and immune rejection (p 5, 1st column). Jun et al, (Curr Gene Ther, 5(2): 249-62, 2005) noted that Type I diabetes results from insulin deficiency caused by autoimmune destruction of insulin-producing pancreatic beta cells and regeneration of pancreatic beta cells from embryonic stem cells may overcome the limited source of islets and transplant rejection if beta cells are regenerated from endogenous stem cells and it is difficult to overcome the persisting hostile beta-specific autoimmune response that may destroy the regenerated beta cells (abstract). Colman (Seminars in Cell & Developmental Biology, 15: 337-345, 2004) while reviewing the state of the art of pancreatic islet cluster cell transplantation reports that STZ treatment can greatly reduce autoimmune destruction in non-obese diabetic (NOD) mice and the undoubted stimulation of recovery may have more to do with modulation of the autoimmune destruction seen in NOD mice than with any direct or indirect effects on pancreatic progenitor cells (p 343, 2nd column). Furthermore, Colman noted that unfortunately, it is often difficult to compare different experimental findings because STZ treatments vary so much in severity, and the degree to which endogenous islets are destroyed is often unclear. This can lead to exaggeration of the functional contribution made by the transplanted cells. In addition, interpretation of results seen in the NOD model should be tempered with the fact that the

etiology and pathobiology of this model is not exactly as for Type I in humans. Diabetes cell therapy will require in vitro expansion of cell numbers as well as differentiation and this will generate many challenges before pancreatic cell therapy is approved for use (Colman, p 344, 2nd column). Bonner-Weir (Horm Res, 60(suppl 3): 10, 2003) while commenting on the status of stem cells in diabetes and what has been achieved notes that: "The field of generating new beta-cells from stem cells, either embryonic or adult, is still in its infancy. Each new report has been met with a mixture of excitement and skepticism. With continued efforts and rigorous assessments, hopefully the potential of generating enough new beta-cells from stem cells will be realized" (Bonner-Weir, p 10). Donovan et al, (Nature, 414(1): 92-97, 2001) noted that if pluripotent stem cells derived from human embryos behave like their counterparts from mice, they could be used to treat a wide variety of human diseases, particularly those in which specific cell types such as beta-islet cells have been lost or disabled, but, the reality is that it is questionable whether the results of studies in animal models suggest pluripotent stem cells can be used to correct disease phenotypes and major hurdles remain to be overcome P 92, 1st column).

It is very clear from the art of record that the state of production of functional mammalian pancreatic islet like insulin secreting cell clusters ex vivo for transplantation therapy of a mammalian patient having pancreatic islet function disorders or Type I diabetes is unpredictable, undeveloped and a therapy of the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations for having pancreatic islet function disorders or Type I diabetes raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art for producing said cells for pancreatic cell therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to

practice the invention as claimed for treating pancreatic islet function disorders and/or Type I diabetes without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production a functional mammalian pancreatic islet like insulin secreting cell clusters ex vivo, particularly for pancreatic islet cluster cell therapy, the lack of direction or guidance provided by the specification for the production a functional mammalian pancreatic islet like insulin secreting cell clusters ex vivo, particularly for pancreatic islet cluster cell therapy, the absence of working examples that correlate to the treatment of pancreatic islet function disorders and/or Type I diabetes, the unpredictable state of the art with respect to the production a functional mammalian pancreatic islet like insulin secreting cell clusters ex vivo, particularly for pancreatic islet cluster cell therapy, the undeveloped state of the art pertaining to the treatment of pancreatic islet cluster cell therapy, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 4 recites the limitation "the obtained cell cluster" in line 1. There is insufficient antecedent basis for this limitation in the claim. It is noted that preceding claims 2 and 3 recite embryonic bodies.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 9-10 are rejected under 35 U.S.C. & 102(a) as being anticipated by Lumeslsky et al, (Science, 292: 1389-1394, 2001).

Lumeslsky et al, teaches embryonic stem cells to progressively differentiate and secrete insulin (p 1389-1394). Lumeslsky et al, teaches that the cells self-assemble to form three-dimensional cell clusters of insulin secreting cells similar to pancreatic islets (p 1389-1394).

With respect to claim 9, Lumeslsky et al, teaches mouse ES cells induced into functioning insulin secreting cells by expansion of ES cells, generation of embryoid bodies, selection of cells, expansion of pancreatic endocrine progenitor cells and induction of differentiation and insulin secreting clusters (p 1390 1392).

With respect to claim 10, Lumeslsky et al, teaches islet clusters release insulin in response to glucose (p 1390-1392).

7. Claims 1-6 are rejected under 35 U.S.C. & 102(e) as being anticipated by Thomson et al, (US 6,602,711).

With respect to claim 1, Thomson et al, teaches a method of making embryoid bodies from primate embryonic stem cells (columns 2-6). Thompson et al, teaches culturing the primate embryonic stem cells together with feeder cells and in media containing leukemia inhibitory

factor (LIF) and once colonies are removed from the tissue culture plate, the ES cells remain in suspension during further emryoid body formation (column 3-4).

With respect to claim 2, Thomson et al, teaches the medium for used for the culturing of embryoid bodies comprises 20 ng/ml of LIF (which falls within the range of 100-1000 U/ml) as indicated by reference by incorporation.

With respect to claim 3, Thomson et al, teaches the medium for used for the culturing of embryoid bodies comprises 20 ng/ml of bFGF as indicated by reference by incorporation.

With respect to claim 4, Thomson et al, teaches the medium used for culturing the embryoid bodies fro expansion was serum-free (column 4).

With respect to claim 5, Thomson et al, teaches that in the instant case the embryoid bodies produced were functional and stained positive for neural cell adhesion molecules (column 5). However, Thomson et al, did not test their cultured embryoid bodies for insulin secretion, as did the applicant for their cultured embryoid bodies.

With respect to claim 6, Thomson et al, teaches the medium for culturing and expanding embryoid bodies is serum-free (column 4).

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram

R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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